APPENDIX S

European Patent Office Decision dated March 22, 2005

FACTS AND SUBMISSIONS

The grant of European Patent no. 0 830 142 based upon European Patent application no. 96915746.0 and claiming priority from US application 440750 filed on 15.05.1995 was mentioned in the European Patent Bulletin 2002/07 on 13.02.2002. Proprietors of the patent (P) are Boehringer Ingelheim Corp. of Missouri, USA.

An opposition against the patent was filed on 13.11.2002 by Wyeth of New Jersey, USA (O).

The patent as granted contains claims 1 to 16 of which claims 1, 4, 5 and 13 are independent claims.

CLAIM 1:

1. A vaccine composition comprising live porcine reproductive and respiratory syndrome (PRRS) virus in a modified and substantially avirulent form and mixed with a pharmacologically compatible carrier agent, said modified and substantially avirulent virus being ATCC-VR2332 virus passaged at least 70 times in cell culture of the monkey kidney cell line MA-104 such that when the modified and substantially avirulent virus is administered to a swine or other mammal prone to PRRS, it fails to cause clinical signs of PRRS disease but is capable of inducing an immune response that immunizes the mammal against pathogenic forms of PRRS.

Claim 4 concerns the use of the passaged virus, claim 5 concerns a method of producing the passaged virus and claim 13 concerns a vaccine obtainable by the method of claim 5.

Together with their notice of opposition, O submitted one single document EP-A-0 529 584 which is designated D1 and requested that all documents mentioned on the front page of the opposed patent be introduced into the opposition proceedings as well. O's main request was stated as being revocation of the patent in total under Article 100(a) EPC because the subject-matter of the patent lacked novelty and inventive step. As auxiliary request, O mentioned oral proceedings, in case the opposition division considered the maintenance of the patent in any form whatsoever.

With letter of 14.07.2003, P requested maintenance of the patent in the form as granted and as auxiliary request, oral proceedings.

On 20.02.2004 the OD issued summons to oral proceedings to take place on 24.11.2004. The summons contained the OD's preliminary opinion on the patentability of the claimed subject-matter, namely that claims 1, 4 and 13-15 lacked novelty and claims 2-3 were not inventive, whereas claims 5-12 and 16 were considered novel and inventive. As part of its reasoning, OD pointed to the Board of Appeal decision T977/93.

With letter of 17.09.2004, O filed further observations why the subject-matter of claims 5-12 and 16 did not involve an inventive step. In particular, O commented that P's arguments in favour of inventive step showed that the patent was insufficiently disclosed and considered that an insufficiently disclosed patent should not be maintained even if Article 83 had not been raised as a ground of opposition. In support of the inventive step arguments, O cited and forwarded two documents which had been cited in the Board of Appeal proceedings T977/93.

With letter of 22.09.2004 (ie before the Rule 71a time limit), P forwarded a declaration by Professor Murtaugh together with an exhibit showing animal test data of samples of vaccine viruses. The declaration stated that, in a virus passaged 70 times, the shedding properties were eliminated and that the non-shedding was a reproducible effect.

O replied to P's observations with letter of 19.11.2004 and asked the OD to exercise its discretion under Article 114 to raise Article 83 as a ground of opposition, in accordance with G10/91, if the statements made in the declaration by Prof. Murtaugh were wrong. In addition, O announced that B.L.Renda and M.Gill would accompany the representative at the oral proceedings.

Oral Proceedings were held as scheduled. In the course of the oral proceedings, OD announced that claims 1, 4 and 13 as granted lacked novelty. In response to this conclusion, P filed an auxiliary request (AR) based on claim 5 of the patent as granted. OD came to the conclusion that the AR met the requirements of Articles 54

and 56 EPC. Finally, OD concluded that Article 83 would not be introduced as a new ground of opposition.

ADMISSIBILITY:

The opposition appears to be admissible because it meets all the requirements of Articles 99(1) & 100 EPC and of Rules 1(1) and 55 EPC. This has not been contested by P.

PROCEDURAL CONCLUSIONS:

TECHNICAL EXPERTS:

None of the parties objected to the technical experts of the other parties and the OD concluded that no reasons existed why the experts should not be allowed to speak at the oral proceedings.

INTRODUCTION OF NEW EVIDENCE:

O wished to introduce the document D64 (a declaration) cited in T977/93 during the oral proceedings. As part of their oral submissions, O was given the opportunity to explain the relevant disclosure of the document (see minutes of the oral proceedings). In view of the fact that the declaration concerned a different virus and a different case and in view of the relevancy of the parts of the document outlined by O as being the most relevant parts, OD came to the conclusion that the document was not sufficiently relevant for it to be introduced into the present proceedings after the Rule 71a time limit.

INTRODUCTION OF AUXILIARY REQUEST:

During the oral proceedings, O objected to the introduction of the auxiliary request into the proceedings. The OD found that the auxiliary request differed from the main request only in the deletion of claims and therefore cannot take O by surprise and O certainly would not need any extra preparation in order to prepare the discussion of the auxiliary request since the claims of the auxiliary request were already present in the main request. The filing of the auxiliary request, even if taking place after the Rule 71a time limit, was therefore accepted by the OD.

FRESH GROUND OF OPPOSITION:

During oral proceedings, O wished to introduce Article 83 as a fresh ground of opposition. P objected to the introduction of this ground of opposition. OD found that a fresh ground of opposition may be introduced by an OD under Article 114(1) EPC only if the ground is sufficiently relevant to be likely to prejudice the maintenance of the patent (see G10/91). In the present case, O argued that the Declaration of Prof.Murtaugh which stated that the virus of D1 was unsuitable as a vaccine cast doubt on whether the virus of the opposed patent was suitable as a vaccine and therefore whether the invention was sufficiently disclosed. In addition, O mentioned that the absence of an upper limit to the number of passages meant that the invention could not be performed insofar as the number of passages are above the passage level shown in the working examples of the opposed patent (ie 75 times).

The OD finds that the statement of Prof.Murtaugh concerns the virus of D1 and concerns the fact that the virus of D1 is shedding and therefore is not perfect as a vaccine virus. In the absence of further details, this cannot cause OD to find it likely that the opposed patent is insufficiently disclosed for this reason.

With respect to virus passaged more than 75 times, O has not provided any proof that it is not possible to isolate viruses with the desired characteristics from virus cultures passaged more than 75 times and OD therefore did not have any reason to consider it likely that the opposed patent is insufficiently disclosed on this basis.

Thus, OD concluded that there was no reason to introduce Article 83 as a ground of opposition into the proceedings.

REASONS FOR THE DECISION:

MAIN REQUEST:

NOVELTY:

Claim 1:

In the notice of opposition, O mentioned that D1 disclosed a live SIRS virus, ATCC-

VR2332, which was modified by passaging (p.6, l.12-14 and claim 8) and that the example in D1 showed passaging 25 times at 35-37°C and 12 times at 31°C. O continued that the passaging in D1 was carried out in MA-104 kidney cell line (p.6, l.42-43 and claim 7) and that the passaged virus was substantially avirulent since it did not cause symptoms of SIRS after challenge (claims 2 & 4, p.5, l.57-p.6, l.1; p.6, l.4-5). Finally, O mentioned that the vaccine composition contained virus together with a pharmaceutically acceptable carrier (claim 2).

Moreover, O, based on an interpretation of D1 as disclosing a broad-range of passages for attenuating the PRRS virus because the wording used in D1 is general and open-ended (ie it suggests that the virus be passaged for attenuation) (see claim 8), continued that D1 disclosed at least 70 passages of the PRRS virus. Thus, O considered that the feature "passaged at least 70 times" would have to be considered a novel selection in order that claim 1 could be considered novel over D1. However, O rejected this possibility because 70 times did not represent a narrow selection and because the limit of 70 passages was clearly arbitrarily chosen.

In their letter of reply of 14.07.2003, P argued that D1 did not disclose passaging 70 times (the skilled person would not understand the mention of passaging in claim 2 of D1 as extending to the disclosure of a range from one single passage to an infinite number of passages because the skilled person would understand that further passaging may result in undesirable characteristics and loss of desirable characteristics). Present claim 1 was therefore not anticipated by D1. However, P continued that, even if seen as a selection invention, claim 1 would be novel over D1 because at least 70 times was not an arbitrarily chosen limit, but represented the first number of passages at which all the desired characteristics were retained including the attribute of non-shedding.

With respect to the EPO Board of Appeal decision T977/93, P added in the letter of 22.09.2004 that T977/93 concerned a case in which the Board of Appeal was of the opinion that it was impossible to correlate the genetic modifications of the prior art virus to the number of passages, whereas in the present case it was the claimed virus which was defined by the number of passages. In the present case, P explained that it was an inherent feature of the claimed virus that it did not shed. This was shown to be a reproducible effect in the declaration by Prof.Murtaugh. According to

the test data shown in the Exhibit annexed to the said declaration, virus, which was warm- or cold-passaged 50 times, exhibited shedding.

O mentioned that the CCV claimed in T 977/93 had different properties from the PRRS virus of the opposed patent (ie it mutated more quickly) and that the skilled person would therefore have less prejudice against passaging the virus further. The OD finds that the unpredictability of the genetic changes in the virus must be the same whether the virus forms part of the prior art or is claimed. In addition, there is no reason to believe that the speed with which mutations occur in the passaged virus influence the predictability of the mutations.

The OD finds in agreement with P that D1 does not disclose a broad range of passages, but rather passaging as a means of attenuating (see claim 8) and one single example of attenuation in which the virus is passaged exactly 37 times. Thus, D1 does not teach passaging at least 37 times and the claimed method cannot be considered a selection of a narrow range from within a broad range disclosed in D1. D1 therefore does not disclose a method of passaging of a virus in which the virus is passaged at least 70 times.

However, the OD finds that the difference in number of passages indicated in claim 1 does not render the claimed subject-matter novel. P argues that it is an inherent feature of a PRRS virus passaged 70 times that it is non-shedding and bases the reproducibility of this finding on the experimental data shown in the Exhibit attached to the Declaration by Prof.Murtaugh. However, these data doo not concern several PRRS viruses each passaged independently 70 times, but show that samples of one PRRS virus culture passaged 70 times do reproducibly not show shedding when administered intramuscularly to a group of pigs.

In the absence of any specific selection pressure during the passaging and in view of the fact that genetic changes which occur during passaging are to a large extent unpredictable (see eg T 977/93 #6, last sentence and also P's letter of reply 14.07.2003 in which it is stated that the skilled person would know that further passaging could cause desirable characteristics of the virus to appear and disappear (p.5, 2nd par., penultimate sentence)), the OD comes to the conclusion that the

number of passages which the virus undergoes does not define the nature of the virus and that the virus resulting from passaging cannot be predicted on the basis of the number of passages carried out in a specific cell line. It is therefore unlikely that all culturing experiments, in which the PRRS virus is passaged 70 times starting from the original virus, would lead to a virus which does not shed. Thus, the OD does not agree with the P that the non-shedding nature of the virus is an inherent feature of the virus passaged 70 times.

The OD is therefore of the opinion that the virus used in the composition of claim 1 is therefore defined only by the other features of claim 1, namely as being a

1) porcine reproductive and respiratory syndrome (PRRS) virus in a modified and substantially avirulent form, which

2) when administered to a swine or other mammal prone to PRRS, it fails to cause clinical signs of PRRS disease, but which

3) is capable of inducing an immune response that immunizes the mammal against pathogenic forms of PRRS.

In the notice of opposition, O outlined (see above) that the virus of D1 also possesses these features.

As discussed above, P pointed out that the virus passaged at least 70 times, when administered to the mammal, had all the desirable characteristics of a virus for vaccination, including the feature that the mammal is not shedding viruses, whereas the virus of D1 shows shedding (see page 4, last par. of P's letter of 14.07.2003).

However, the OD finds, in agreement with O, that the skilled Reader, in view of the teaching in the opposed patent, would not understand the non-shedding as belonging to the clinical signs to which claim 1 refers. On the contrary, this is a feature which the opposed patent wishes to obtain via cold adaptation see [0110]. The virus exemplifying the invention, namely ATCC-VR 2495, is obtained in the patent by "warm" passaging and the skilled reader would therefore not believe that this virus had this characteristic and would therefore not believe shedding to be a clinical sign which the virus as defined in claim 1 must not cause.

In addition, as pointed out by O, shedding is a transmission of virus and not a sign of disease and therefore is not considered a clinical sign in the typical understanding of this term.

P has not disputed that the virus of D1 possesses the above features 1) and 3).

Thus, the virus of D1 appears to possess the features 1)-3) and the OD, therefore, concludes, in view of the established case law that claims for products defined in terms of processes for their preparation have to fulfil the requirements of patentability and that this is independent from the patentability of the processes (see Guidelines C-III 4.7b), that claim 1 lacks novelty over D1.

Claim 4:

The second medical use of claim 4 is disclosed in D1 (see claim 4) and claim 4 therefore does not appear to be novel for the same reasons as claim 1. P did not bring any separate arguments in favour of novelty of claim 4.

Claim 13:

The OD concludes that the subject-matter of claim 13 lacks novelty for the same reasons as claim 1. P did not bring any separate arguments in favour of novelty of claim 13.

AUXILIARY REQUEST:

NOVELTY:

During oral proceedings (see minutes thereof), O formulated a novelty attack on claim 1 of the auxiliary request. However, throughout the written proceedings, O has not raised any novelty objections against the claimed subject-matter because the features that a stabilising agent is added to the virus culture and the virus culture is lyophilised are not explicitly disclosed in D1. The OD still finds that these features are not disclosed in D1 and therefore considers claim 1 of the auxiliary request novel at least for this reason.

INVENTIVE STEP:

Difference to D1:

O argues that the subject-matter of claim 1 differs from D1 by the stabilisation and lyophilisation features mentioned above. According to O, claim 1 therefore lacks an inventive step in view of D1.

However, as discussed above under novelty of claim 1, O's argumentation is based on an interpretation of D1 as disclosing a broad-range of passages for attenuating the PRRS virus because the wording used in D1 is open-ended.

However, as explained above, the OD finds that D1 does not disclose a broad range of passages and does not disclose passaging at least 70 times.

Thus, the OD is of the opinion that claim 1 differs from D1 in that the virus is passaged at least 70 times and in that a stabilising agent is added to the virus culture and the virus culture is lyophilised.

Objective technical problem:

As explained above, OD is of the opinion that a certain number of passages cannot provide the virus with an inherent feature due to unpredictability of the genetic changes occurring during passaging. However, OD accepts that the likelihood that the virus has certain characteristics may be a function of the number of passages to which the virus is exposed.

P has provided an Exhibit showing that pigs vaccinated intramuscularly with a virus passaged 70 times do not shed viruses, whereas viruses passaged 37 times, as in D1, are shed when administered intranasally. Although the way of administration may play a role in the difference in shedding behaviour of the viruses, as pointed out by O, P argued that the technical problem was the provision of a method for obtaining non-shedding PRRS viruses.

O argued that this problem represented a change of technical problem which was not supported by the original application which stated the problem as being the provision of an efficient vaccine which can eliminate or ameliorate the effects of PRRS.

The OD agrees with P (see also Case Law I.D.4.5, 4th Ed.) that the technical problem may be reformulated if the problem can be deduced from the application as filed. In the present case, the elimination of shedding is mentioned as an objective (see the last paragraph of the description). Though cold passaging is mentioned as the means for providing non-shedding viruses, there is no doubt that the skilled person would understand the last paragraph as non-shedding being an objective which it is desirable for the virus of the invention to possess, even if it does not fall within the clinical signs to which claim 1 refers (see above). The said technical problem is therefore deducible for the skilled person from the original application.

O provided the additional argument that the example in the patent showed that the interval between 70 and 75 passages provided a safe and efficient virus, but that, insofar as the claim related to viruses passaging more than 75 times, the properties of the resulting viruses were not at all clear, especially in view of P's argument that the mutations in viruses were unpredictable. Therefore, no technical problem had been solved and the claim was not inventive. O referred to T939/92 in this respect.

OD is of the opinion that no data has been provided by the parties which could show that the possibility of obtaining viruses which do not shed does not exist if the virus culture is passaged more than 75 times. Therefore, the OD, in view of the lack of predictability of the genetic mutations arising during passaging, finds that the technical problem objectively solved by the claimed method must be formulated as the provision of a method, with which it is possible to obtain viruses that do not shed when administered intramuscularly.

Is the solution obvious?

The OD agrees with O, and this has not been contested by P, that the features:

1) adding a stabilising agent to the virus culture and
2) lyophilising the virus culture

are routinely employed in methods of producing vaccines.

Thus, the discussion on obviousness concentrated on the feature "passaging at least 70 times".

In this respect, O provided the following arguments:

Firstly, it would be clear to the skilled person in view of the general teaching in D1 that any number of passages was suitable for producing a virus suitable as vaccine. O argued further that T977/93 related exclusively to CCV vaccine and that CCV was a special case because, as outlined in declarations submitted in that case, only a limited number of passages could be made before CCV underwent undesirable mutations. and that D1 showed that the PRRS virus could be passaged a high number of times (37 times) without having undesirable mutations. Thus, there was no

prejudice in D1 against increasing the number of passages. On the contrary, the skilled person would expect to get a better attenuated vaccine by increasing the number of passages and the skilled person would therefore be motivated to increase the number of passages in order to arrive at an alternative safe and efficient vaccine.

Secondly, cold adaptation was a well-known method to produce viruses which do not shed and it would therefore be obvious to use cold-passaging in order to obtain a virus which did not shed.

OD finds that D1 does not mention shedding of PRRS as a problem of the virus vaccine and the skilled person therefore would not be motivated based on D1 to increase the number of passages in order to solve the technical problem identified above. Even if the skilled person from his general knowledge knew that shedding was a problem with viral vaccines, the known solution to this problem is cold adaptation and nothing in the prior art suggests that the virus be passaged at least a further 33 (70 - 37) times cold in order to eliminate shedding. On the contrary, D1 discloses that the virus is passaged 12 times cold and the skilled person would therefore believe that shedding was eliminated in the virus of D1.

In addition, the OD is of the opinion that the skilled person would not have arrived at the method of claim 1 while solving another problem in which case the absence of shedding would have been considered a bonus effect. As argued by O (see letter of 19.11.2004, page 2, 2nd and 3rd paragraphs), D1 discloses a virus which provides a vaccine that does not cause any clinical signs of disease and protects efficiently the vaccinated pigs. The skilled person would therefore not have any incentive to increase the number of passages in order to provide a virus with improved attenuation.

OD therefore concludes that the method of claim 1 would not be obvious to the skilled person in view of the prior art and that the subject-matter of the auxiliary request therefore meets the requirements of Article 56 EPC.

DESCRIPTION:

P filed amended pages 3 and 3a of the description. O did not have objections against the amendments and OD agrees that they are acceptable.

DECISION:

OD decides that the subject-matter of the auxiliary request and amended description pages meets the requirements of the EPC and that the opposed patent may be maintained in amended form (Article 102(3) EPC).